



The evolution of associative learning: A factor in the Cambrian explosion

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ABSTRACT

The Cambrian explosion is probably the most spectacular diversification in evolutionary history, and understanding it has been a challenge for biologists since the time of Darwin. We propose that one of the key factors that drove this great diversification was associative learning. Although the evolutionary emergence of associative learning required only small modifications in already existing memory mechanisms and may have occurred in parallel in several groups, once this type of learning appeared on the evolutionary scene, it led to extreme diversifying selection at the ecological level: it enabled animals to exploit new niches, promoted new types of relations and arms races, and led to adaptive responses that became fixed through genetic accommodation processes. This learning-based diversification was accompanied by neurohormonal stress, which led to an ongoing destabilization and re-patterning of the epigenome, which, in turn, enabled further morphological, physiological, and behavioral diversification. Our hypothesis combines several previous ideas about the dynamics of the Cambrian explosion and provides a unifying framework that includes both ecological and genomic factors. We conclude by suggesting research directions that would clarify the timing and manner in which associative learning evolved, and the effects it had on the evolution of nervous systems, genomes, and animal morphology.

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1. Introduction

The “Cambrian explosion” is one of the great riddles of evolution. The fossil evidence suggests that in a geologically very short period from around 545–520 million years ago (Mya), most metazoan phyla first appeared and diversified (Valentine, 2004; Marshall, 2006; Brasier, 2009). Although paleontologists agree that there was a very rapid increase in animal size and morphological diversification during this epoch, controversies persist about its causes and the nature of the evolutionary events that preceded it. Fortey (2001) claims that the Cambrian explosion is an artifact of fossilization: the morphological complexity of animals discovered during the early Cambrian points to a necessary existence of morphologically complex ancestors in the pre-Cambrian, fossils of which have not been found because they were of small size and lacked hard parts. Levinton (2008), who reviewed the many open questions presented by the Cambrian explosion hypothesis, summarized molecular data that suggests that Cambrian animal phyla had ancient pre-Cambrian bilaterian ancestors, whose (presumably) small, soft-bodied fossils have not yet been found. Brasier (2009), on the other hand, contends, on the basis of the pre-Cambrian

fossil record and fossilization processes, that a full-blown explosion of animal phyla did occur during the Cambrian, and that the absence of earlier ancestors in pre-Cambrian rocks, when fossilization conditions were excellent, does indicate the actual absence of pre-Cambrian bilaterian ancestors. Developmental considerations led Valentine et al. (1999) to suggest that minute bilaterian animals were present during the Ediacaran era, possibly 570 Mya, preceding the larger benthic Cambrian bilaterians, and that extensive morphological and genomic re-patterning occurred during the early Cambrian. Peterson et al. (2008) also argue for an Ediacaran origin of bilaterians: on the basis of analyses of new molecular data and several comparative methods, they conclude that bilaterians emerged during the Ediacaran era, and it was their emergence that established “the ecological and evolutionary rules” that enabled the subsequent Cambrian explosion. Nevertheless, whatever their interpretation of molecular and paleontological data, almost all those who study this period agree that a remarkable ecological and morphological diversification occurred during the Cambrian, and that the nature and causes of this diversification are pertinent and important questions (Valentine, 2004, p. 195).

The Cambrian seems to have been a unique junction-period during which the consequences of the biological, climatological, tectonic, and geochemical events that happened in the preceding Ediacaran period came together and interacted. The environmental events include: increases in oxygen concentration, beginning ~635 Mya, which led to diversification of the Ediacaran

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fauna and the appearance of the first calcifying metazoans ~548 Mya (Fike et al., 2006; Canfield et al., 2006); pulses of global warming, the result of methane release associated with true polar movements, which led to increased nutrient cycle and productivity (Kirschvink and Raub, 2003; Butterfield, 1997); changes in the chemical constitution of the oceans that coincided with the Cambrian explosion, and may have spurred the evolutionary changes in marine biota (Brennan et al., 2004). All these changes probably had effects that were crucial for the occurrence of the Cambrian explosion. However, these global processes do not explain why a central (though certainly not exclusive) aspect of the Cambrian explosion was dramatic morphological diversification within the animal kingdom. An explanation of this aspect of the Cambrian explosion must incorporate developmental and ecological factors specific to

bilaterians, and point to the genomic organization which has made this possible. Following the model suggested by Newman and Bhat (2009), we believe that for such morphological evolution to occur, extensive developmental plasticity must have characterized the pre-Cambrian bilaterians, and that this plasticity was the outcome of the self-organizing properties of developing organisms as they responded to environmental and mutational changes. We regard such developmental plasticity as a necessary but not sufficient prerequisite for the Cambrian explosion. How, and under what ecological conditions developmental plasticity became manifest, was organized and stabilized, is therefore one of the main questions which need to be considered when the Cambrian explosion is studied.

Many hypotheses attempt to explain the biological changes underlying the observed explosion of morphological forms during

Table 1

Some biological (developmental-genomic) innovations suggested as explanations or prerequisites of the bilaterian Cambrian explosion.

Causes of innovation	Contribution to the Cambrian explosion	References
Developmental/ecological innovations or prerequisites		
Macroscopic predation	Evolution through arms races among predators and prey, leading, among other things, to burrowing and the evolution of hard parts	Reviewed by Bengtson (2002) and Dzik (2005)
Evolution of anus and directed movement	Improved sorting of food and waste, anterior–posterior directed movement, leading to diversification	Cavalier-Smith (2006)
Appearance of set-aside cells	Complex morphologies arose through the evolution of specifications for adult body plans within set-aside cells (sequestered in simple ancestral lineages). Set-aside cells are assumed to have been homologous among some phyla, so the common ancestors of these phyla had body plans similar to an ancestor of their larvae	Davidson et al. (1995) and Peterson et al. (1997)
Appearance of a nervous system	Improved motor coordination; learning led to developmental and ecological complexity	Stanley (1992) and Cabej (2008)
Appearance of consciousness	Emergent processes at the quantum-mechanic level, involving microtubules which led to increased behavioral and ecological complexity	Hameroff (1998)
Appearance of visual perception	Arms races between predator and prey species; invasion of new niches	Reviewed in Parker (2003)
Burrowing (associated with an anterior–posterior axis)	Burrowing animals changed the ocean soil by mixing it, and led to the recycling of organic matter and pushing downward of phosphate and other minerals. This enabled rapid animal evolution (and also altered the preservation conditions, preventing the ready fossilization of fragile cells and tissues)	Brasier (2009)
Emergence of associative learning	Expansion and formation of new niches; arms races and cooperative alliances; led to the emergence of experiencing	Ginsburg and Jablonka (2007b, 2010), this paper.
Genomic causes or prerequisites		
Dynamical patterning modules (DPMs)	Generation of morphological novelties through the mobilization by developmental core genes of physical processes in cell aggregates (cohesion, viscoelasticity, diffusion, etc.)	Newman and Bhat (2009)
Changes in the genetic regulatory networks that organize animal ontogeny occurring in animals with relatively loose developmental organization	Differences among phyla	Knoll and Carroll (1999) and Arthur (2000)
Establishment of kernels (inflexible sub-circuits that perform essential upstream functions in building body parts) of gene regulatory networks (GRNs)	Morphological differences among animal phyla based on common, ancient GRNs	Erwin and Davidson (2002) and Davidson and Erwin (2006)
Mobilization of transposable elements	Increase genetic variability, affecting regulation of gene networks	Oliver and Greene (2009) and Zeh et al. (2009)
Stress: Epigenomic stress responses	Increase in selectable variation	Zeh et al. (2009)
Stress: Temperature stress that affected chaperone proteins such as Hsp90	Relaxation of canalization and exposure of previously cryptic variation to selection	Baker (2006)
Stress: Neurohormonal stress leading to epigenomic destabilization	Increased genetic variability, especially of genes expressed in the brain	This paper
MicroRNA accumulation	Increased precision of gene regulation; increased evolvability, (by increasing heritability through the canalizing effects of miRNAs)	Heimberg et al. (2008) and Peterson et al. (2009)
Horizontal gene transfer	Acquisition of new genes for example of skeletonization-related genes that allow establishment and spread of animals with hard parts and leads to arms races and ecological complexity	Mourant (1971)
Extensive hybridization	Inter-species hybridizations expanded the genome and morphological possibilities; led to the origin of larval forms	Williamson (2006)
Duplications of genes/genomes	Duplicated genes diverged and new functions evolved	Lundin (1999); but see Miyata and Suga (2001)

the Cambrian (Valentine, 2004; Marshall, 2006; Levinton, 2008). Table 1 provides a non-exhaustive list, showing different hypotheses ranging from those having some empirical support to those that are, at present, entirely speculative. The introduction of yet another hypothesis is only justified if it is more economical than other hypotheses, has a greater explanatory power, or if it brings previous hypotheses and data together within a unified framework. We believe that no single event can explain the Cambrian explosion. It is far more plausible that interactions among several abiotic and biotic factors created a positive evolutionary feedback-loop that culminated in the explosion of bilaterians. A transition from the nearly two dimensional benthic existence of the pre-Cambrian animals to the three dimensional world of burrowing and swimming animals, was a crucial part of this process, opening up enormous, initially unconstrained, ecological opportunities (Peterson et al., 2008). As Cabej (2008) has stressed, the evolution of the central nervous system (CNS) and the ability to memorize past experiences played a major role in the Cambrian explosion. We put forward the more specific suggestion that associative learning was one of the key biological innovations that contributed to this evolutionary feedback-loop, and that its emergence enabled behavior-driven phenotypic adjustments (Ginsburg and Jablonka, 2007b, 2010), which were followed by the re-organization of the genetic architecture through genetic accommodation and were associated with stress-induced epigenomic changes. Our hypothesis incorporates several previous explanations, which are pointed to in Table 1 as special cases and preconditions, and suggests that accompanying and reinforcing regulatory genomic changes occurred as a result of neurohormonal stress responses.

2. The evolutionary origins of associative learning

Associative learning is a behavioral modification, dependent on reinforcement, involving new associations between different sensory stimuli, or between sensory stimuli and responses (see Razran (1971) and Abramson (1994) for comprehensive reviews). At the neural level, it involves the modification or formation of connections among neural circuit elements that link sensors and effectors. The stimuli that become associated can be incidental or even completely artificial ones, as well as biologically important stimuli such as those that are typically linked to basic homeostatic and reproductive functions, to the animal's own responses, and to the environmental contexts in which particular stimuli and responses occur. On the basis of past memorized experiences, associative learning allows anticipation of future events and rewards, and discrimination among different classes of cues.

Two major types of associative learning – classical (Pavlovian) conditioning and instrumental or operant conditioning – are commonly distinguished in the learning literature. Classical conditioning is a modification of behavior in which a new “neutral” stimulus is paired with a stimulus that already elicits a particular response (either because it is innate or because it was learnt at an earlier stage). An organism exposed repeatedly to pairs of the “neutral” and original stimuli will eventually respond to the “neutral” stimulus alone. For example, a dog normally salivates at the smell of food; but if it hears a bell just before smelling the food, it will learn to associate the sound with being fed, and salivate when it hears the bell. Many types of classical conditioning and many combinations of different types of learnt associations have been described (Abramson, 1994).

Instrumental (or operant) conditioning is a form of associative learning in which the *actions* of the organism are reinforced by their consequences. For example, a hungry rat, moving restlessly in a box with a lever, accidentally presses the lever and receives

a pellet of food; if this happens a few times, the hungry rat will press the lever more and more often. An association is formed between the rat's response (lever pressing) and a special consequence of this response (food, the reinforcement). As with classical conditioning, there are many types of instrumental learning. When the motor behavior that becomes associated with reward or punishment is novel and non-stereotyped (e.g. pressing a lever or jumping through a burning hoop), and hence is a behavior that is *not* part of the animal's preexisting behavioral repertoire, conditioning is called operant, rather than instrumental.

Psychologists consider classical and instrumental/operant associative learning to be the most fundamental form of learning (Skinner, 1981) and regard it as the basis of all animal cognition. Macphail (1987) and Macphail and Bolhuis (2001), for example, argued that learning in all vertebrate species, from goldfish to chimpanzee, can be explained by a general mechanism of associative learning. The importance of associative learning has not escaped the notice of philosophers. Dennett (1995), for example, pointed out that once associative learning is in place, a new type of adaptive adjustment is possible: animals can make adaptive changes in their behavior ontogenetically (during their life time), whereas previously they could occur only phylogenetically (during evolutionary time), through the differential survival and reproduction of individuals. This is a quanta leap in terms of adaptability. But despite the general appreciation of its importance, associative learning has received very little attention from evolutionary biologists. Although there are some speculations about the route leading from sensitization and habituation to associative learning (Wells, 1968; Razran, 1971), there are no studies addressing the evolutionary origin of associative learning and its relation to the evolution of the CNS.

Animals in the metazoan groups that first appeared during the Cambrian were relatively large, and many have a well developed CNS with a distinct brain (Stanley, 1992; Cabej, 2008). The majority of the extant representatives of the Cambrian metazoan phyla that have been tested for their ability to learn exhibit associative learning (Corning et al., 1973; Abramson, 1994), although there are many animal groups whose learning abilities have not been studied. The distribution of associative learning depicted in Fig. 1 suggests that it is an ancient feature of the Nephrozoa (deuterostomes and protostomes), which either appeared in their common ancestor, or evolved in parallel in several groups because the conditions for its ready emergence were already present.

What were the neural-anatomical correlates of associative learning? What, in particular, is the relationship between the evolution of the CNS and the evolution of associative learning? The answer to this question is not clear, and several different scenarios are possible: associative learning preceded the evolution of a CNS, arose in conjunction with it, or followed it. The latter two possibilities seem more plausible than the first one, since at present there is no evidence for animals lacking a CNS exhibiting associative learning. The evolution of the CNS, which is an intensely researched topic, is, however, controversial (Miller, 2009). For example, while according to Reichert (2009), Arendt et al. (2008) and Denes et al. (2007) molecular mechanisms involved in building the CNS of extant bilaterians and many details of the architecture of the CNS were probably present in their common urbilaterian ancestor, others favor the view that the centralization of the nervous system and even the appearance of neurons originated independently in multiple lineages (Lowe et al., 2006; Moroz, 2009).

Although we believe that information about the evolution of associative learning may contribute to our understanding of CNS evolution, our hypothesis does not depend on whether or not the

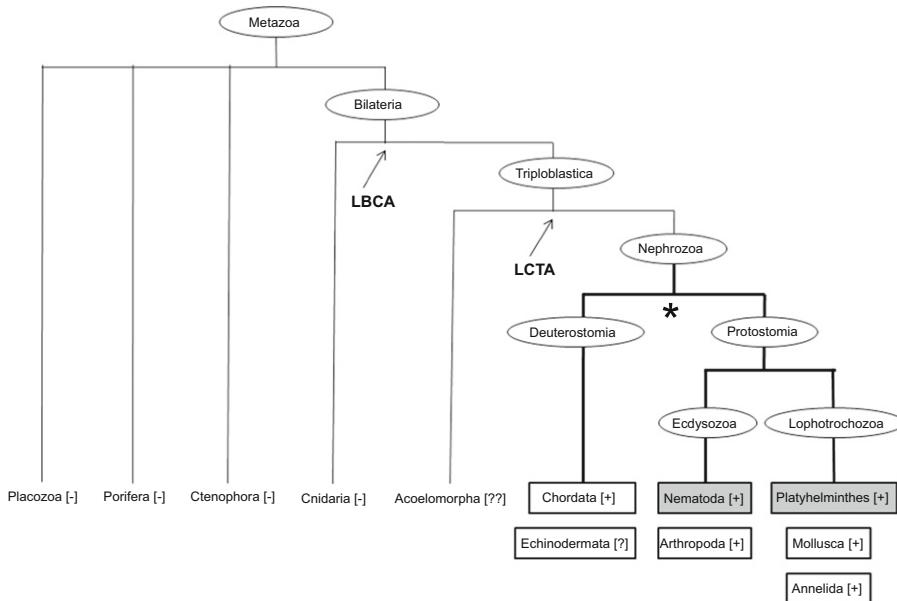


Fig. 1. Associative learning in the evolution of animals. The phylogenetic tree (based on Baguñà et al., 2008) shows the last common bilaterian ancestor (LCBA) and the last common triploblastic ancestor (LCTA). Lineages that appeared during the Cambrian explosion are highlighted (thick lines), and the emergence of associative learning (whether in a single lineage or in multiple lineages) is indicated by *, which also marks the beginning of the Cambrian explosion. The occurrence of associative learning in the major taxonomic divisions of metazoans is indicated by a plus sign. The non-triploblastic animals belonging to the taxa in the unboxed groups do not show associative learning, as indicated by minus signs. The first fossil representatives of most triploblastic phyla appear in Cambrian (groups in white boxes) or in post-Cambrian sediments (groups in gray boxes). In echinoderms there is a paucity of information about their ability to learn by association (indicated by ?). Acoelomorphs have not left early fossil records and their learning capacities have not been studied (indicated by ??).

evolution of a CNS accompanied or was followed by the evolution of associative learning, nor does it depend on whether or not the CNS has monophyletic or polyphyletic origin. Our hypothesis does predict, however, that once associative learning had evolved it affected the evolution of the CNS in the lineage/s in which it arose, leading to an increase in brain size and to greater differentiation and integrations among the parts of the CNS. Moreover, as we argue in the next section, our hypothesis favors the parallel evolution of associative learning in different lineages.

Although we are not committed to a particular evolutionary scenario of early animal evolution, we present a plausible phylogenetic tree suggested by Baguñà et al. (2008) showing a general picture of animal evolution and indicating whether or not associative learning has been found in the different taxa (Fig. 1). According to this phylogenetic tree, Cnidaria are a sister group of the triploblastic bilaterians, the bilaterians that have true mesoderm and that include the acoelomorph flatworms. The acoelomorphs are the paraphyletic group, which includes the nematodermatids (not shown in this simplified tree), from which the protostomes and deuterostomes (the Nephrozoa) probably evolved (Baguñà and Riutort, 2004; Baguñà et al., 2008). The view that the acoelomorphs were the ancestors of bilaterians fits with the conclusion of Valentine et al. (1999) that the common ancestors of phyla with set-aside cells had body plans similar to an ancestor of their larvae, and that the body plans of the minute bilaterian ancestors may have resembled those of minute acoelomates and pseudocoelomates. Unfortunately, the learning abilities of acoelomorphs, who like cnidarians and ctenophores have a diffuse nervous system, have not been studied.

As the figure indicates, associative learning has been reported in many nephrozoan groups, including nematodes, arthropods, platyhelminthes, molluscs, annelids, and, of course, chordates (Corning et al., 1973; Abramson, 1994). All the animals for which associative learning is well established have a CNS with a well defined brain. For the echinoderms, which are believed to have

undergone secondary radialization, data are limited, so the level of complexity and the range of associative learning in this group has not yet been established (Willows and Corning, 1973).

Since learning by association dramatically enhances adaptability, we propose that its emergence was an important element in the evolutionary feedback-loop that drove the Cambrian metazoan radiations. For example, associative learning may have been one of the factors contributing to the diversification of antipredatory morphology and behavior (e.g., protective mineralized spines, poison) of Ediacaran protozoans and other microbenthos and microplankton during the Cambrian (Valentine, 2004; Knoll, 1994); since the evolution of associative learning enhanced the efficiency of predation, it is likely that the evolutionary sophistication of some antipredatory responses in these clades followed suit. Our hypothesis can also explain the extinction of Ediacaran organisms that occurred during the early Cambrian (Valentine, 2004): the growth in size of populations of associatively learning bilaterians would have decimated their competitors.

We do not know what the animals belonging to the new phyla that appeared at the beginning of the Cambrian were able to learn. If their ancestors were, as Fig. 1 suggests, small acoel-like bilaterians, they probably manifested some clustering of nerve cells forming a cerebral commissure at the anterior end (Kotikova and Raikova, 2008). A comparison of neurodevelopment and conserved molecular architecture in protostome and deuterostome models suggests that a large part of the spatial organization of the invertebrate and vertebrate CNS was already present in their last common ancestor (Arendt et al., 2008). Such neural centralization allows integration of sensory inputs and coordination of motor outputs between regions, as well as coordinated interactions within regions. It is therefore plausible that the common ancestor could manifest the simple types of non-associative learning seen in cnidarians. The simplicity of the nervous system organization of the acoels and their tiny size

suggest that their learning abilities are unlikely to exceed those of cnidarians, but only the direct study of the learning abilities of acoelomorphs can throw light on this question.

The evolution of associative learning required mechanisms that could partially stabilize newly formed associations between neurons that fire together, so that upon a subsequent stimulation they were more easily and rapidly activated. The basis of this evolution was presumably the molecular memory mechanisms underlying long-term sensitization and habituation, which are present in *all* neural animals, including the cnidarians (Wells, 1968; Razran, 1971); associative learning involved recruiting these mechanisms for stabilizing transient neuronal connections that were formed during successful exploratory behavior (Ginsburg and Jablonka, 2007a).

We suggest that more reliable and flexible memory mechanisms evolved following an increase in size that may have been linked with the increased oxygenation of the sea during the later Ediacaran period, ~548 Mya (Fike et al., 2006). Although the amount of oxygen required for activities such as slow burrowing in mud is low (Budd and Jensen, 2000), swimming and more active movements requires relatively high oxygen levels. High oxygen levels have been shown to be important for sustaining complex ecology (Catling et al., 2005) and for the types of activities assumed to occur in macroscopic Cambrian animals. Crucially, increased oxygenation is important for neural tissues, which are metabolically expensive, so their growth and maintenance was probably increased as the level of oceanic oxygen rose, extending neural connectivity and enabling the formation of new connections. Increased size required better motor and sensory coordination and neural integration, and was associated with bigger, metabolically expensive brains and ganglia. A further benefit of learning occurred as life span (which is likely to have been correlated with size) increased, and animals lived long enough for past events to recur and for their memorization to be worthwhile. We speculate that the new memory mechanisms that evolved as size and life span increased involved the long-term strengthening of synaptic connections among several *different* sensory and motor neural trajectories. The initial stages of associative learning evolution may therefore have required only very simple modifications in the threshold concentrations of molecules that strengthened synaptic connections between newly linked and activated neurons. An increase in the number of connections among groups of co-activated neurons, leading to back and forth signaling (reentry) (Edelman and Tononi, 2000), might have contributed to persistent memory. Such changes may initially have been consequences of the increased metabolism allowed by increased oxygen levels, which only later became stabilized and fine-tuned by congruent genetic changes.

3. The evolutionary effects of associative learning: ecological explosion through the Baldwin effect

The idea that plasticity can drive evolution is a recurring theme in evolutionary biology. Although plasticity (both morphological and behavioral) can slow down evolution, because it makes some hereditary variations invisible to natural selection, when persistent changes in conditions occur plasticity will drive evolutionary change, because selection can readily lead to the stabilization of diverse plastic, developmental responses (Bateson, 2005; Newman et al., 2006; Newman and Bhat, 2009; West-Eberhard, 2003).

The evolution of the plasticity afforded by learning was an important topic of discussion at the end of the 19th century, when it was suggested that if learning enables individuals to adapt to new conditions, those that are better learners will be most likely

to survive and reproduce. Hence, through natural selection, learning capacity will improve, and eventually the selection of chance changes in the lineage's hereditary constitution will result in the behavioral adaptation occurring without learning. This type of process, now known as "the Baldwin effect" (Baldwin, 1896), was generalized by Waddington (1957) and Schmalhausen (1949), who applied it to any adaptive environmentally induced character modification. Waddington called the selection process leading from a stimulus-dependent response to a response that is independent of (or less dependent on) external stimulus "genetic assimilation", and Schmalhausen called it "stabilizing selection". The idea that selection for responsiveness can modulate canalization and plasticity was expanded by West-Eberhard (2003), who argued that any genetic variation, affecting behavior or morphology that contributes to the effectiveness of an adaptive, induced or learnt, developmental response by making it more reliable, rapid, precise, specialized, or more extensively plastic, will be selected. She called the process "genetic accommodation". The role of behavior and learning in evolution through genetic accommodation was emphasized by Bateson (2005) who called it the "adaptability driver". Avital and Jablonka (2000) suggested that genetic assimilation can lead not only to specialization, but also to an increased sophistication of behavioral repertoires, because genetic assimilation releases cognitive-learning resources that allow additional learning. Burtsev et al. (in preparation) have explored the dynamics of this type of effect and shown how learning can lead to innovation and greatly increase the rate of evolution.

The idea that changes in behavior can drive morphological evolution and underlie major adaptive radiations was developed by Hardy (1965), who suggested that some adaptive radiations were the result of the Baldwin effect. In particular, he thought that the dramatic radiations of reptiles, mammals, and birds were driven by their enhanced learning ability. The extent and nature of learning in these groups led to the invasion of new niches and thus to new selection regimes. Wyles et al. (1983) called this guiding effect of behavior on evolution and adaptive radiations "behavioral drive". West-Eberhard (2003), too, attributed a crucial role in adaptive radiations to developmental plasticity, which includes learning. A more radical hypothesis for the role of plasticity in evolution was developed by Newman and colleagues (Newman et al., 2006; Newman and Bhat, 2009; Newman and Müller, 2010). They argued that the morphological, developmental plasticity of pre-Cambrian animals was the basis for the diversification of body plans that occurred during the Cambrian, when many different, initially highly plastic, developmental paths became canalized.

Our suggestion that associative learning drove the Cambrian explosion is based on similar reasoning. Organisms with long-term memory and associative learning had an enormous selective advantage: they were able to adapt ontogenetically to a variety of biotic and abiotic environments and to use new resources. Their learnt behaviors guided where and how they looked for food and protection, how they sought mates, how they reacted to predators and to competitors, and were fundamental to the construction of the niches that they and their offspring inhabited (Avital and Jablonka, 2000; Odling-Smeek et al., 2003). For example, if an animal learnt that food is usually available in a particular area and consequently it tended to stay and reproduce there, its offspring would have the same learning environment and learning opportunities. Natural selection would then favor any physiological or morphological features that improved adaptation to this learning environment. The explosion of new behaviors and new ecological opportunities that followed the evolution of associative learning would have been accompanied by an explosion of new, matching, morphological adaptations. For example, a better

ability of predators to capture prey led to the evolution of protective measures in prey, including hard external skeletons. Associative learning may also have driven the directional evolution of particular sensors. For example, if the presence of a particular type of prey frequently altered patterns of light intensity, this association might have driven the evolution of greater visual discrimination. Rapid evolution of vision and other modalities such as touch, taste and smell, is expected once associative learning has evolved. The evolution of the eye, which Parker (2003) believes drove the Cambrian explosion, was, according to this scenario, just one of the several consequences of the evolution of associative learning, each of which had strong evolutionary domino effects.

Learning-driven adaptation in one lineage inevitably affected interacting species. Thus, as the learning ability of a predator improved, there would have been strong selection for morphological and physiological adaptations (such as protective hard parts, poison, or escape reactions) in its prey species, for stress responses associated with flight and fight, and also for the prey's ability to learn to avoid predators. Although many species were probably driven to extinction by associatively learning species, others evolved countermeasures. Such countermeasures in other bilaterians probably involved specific hormonal and neural adaptations, including, in some cases, long-term memory and associative learning. Consequently, not only did associative learning lead to the radiation of the group in which it emerged, it also led to learning-guided co-evolutionary morphological radiations and to a learning arms-race in some interacting species. We believe that parallel evolution of associative learning was possible because the genetic machinery and developmental networks required for the emergence of long-term memory were already in place in pre-explosion ancestors, and initially only minor modifications in their assembly were required. Hence, the greatly expanded and newly evolved behavioral plasticity that associative learning afforded molded the more ancient morphological plasticity of early bilaterians, and led through canalizing selection, to new, diverse, neural, and morphological characters.

4. Learning-associated neurohormonal stress as a factor in genome evolution

Although the great advantages of associative learning are obvious, and include both the more frequent satisfaction of appetitive behavior (the more ready acquisition of food or mate through guidance of associated cues) and a better ability to cope with antagonistic interactions, associative learning has costs. Since predators and competitors often pose immediate existential threats, associative learning inevitably leads to overreaction, because the animal responds to cues that are sometimes, yet not always, associated with dangers. Overreaction is advantageous as long as the benefits of avoiding actual danger exceed the costs of responding erroneously to perceived danger, which will often be the case with flight reactions, with preparing to fight an adversary, and with focusing attention on sources of potential harm. We therefore expect, and indeed observe, flight responses and a readiness to fight when neither predator nor foes are around. Nesse (2001) has called the logic of these types of overreactions to danger (he focused on flight and anxiety reactions) the "smoke detector principle". Since the cost of encountering "fire" (predator, foe, any other type of potentially grave danger) is very high and the cost of flight from it is relatively low, it is advantageous to flee upon any grave-danger-associated cue ("smoke"), and false alarms are therefore inevitable. However, since these stressful false alarms inevitably

trigger the mobilization of organismal resources, it means that there are considerable costs to associative learning.

In extant animals, perceived stress is managed by a *stress response system*—an evolved and complex set of reactions that ensure survival in the face of environmental insults. It involves the neuroendocrine and immune systems, and a variety of other organs, such as the heart and lungs. In vertebrates, the reaction engages the hypothalamic–pituitary–adrenal axis, but today it is recognized that even in invertebrates like molluscs, which do not possess a hypothalamus, pituitary or adrenal glands, there are parallel neuroendocrine and immune activities that participate in the response to stress (Ottaviani and Franceschi, 1996; Ottaviani et al., 2007; Stefano et al., 2002). Stress response systems manage the extreme destabilized physiological states that animals exhibit following stress. They probably evolved through selection for limiting states of arousal and focused attention, and for restricting the duration and extent of the destabilized physiology. However, even in extant organisms, persistent stress conditions and the accompanying evolved stress responses lead to destabilization: for example, to immunosuppression, which may result in sickness and weakness. Before the stress-managing systems evolved, destabilization was probably much more enduring and had more deleterious effects.

We suggest that in the early Cambrian, as-yet-unmanaged ongoing stress reactions led to *genomic* destabilization: to persistent, widespread, and sometimes heritable changes in gene expression and to DNA re-patterning both in the nervous system and in gametes. Hence, in addition to its role as "an adaptability driver" (Bateson, 2005), which leads to new adaptations through genetic accommodation, associative learning may have had an additional, direct effect on the generation of variation: it increased evolvability because the resulting neurohormonal stress increased the generation of new heritable genomic variation.

The nature and causes of genomic changes that underlay the morphological explosions in bilaterians during the Cambrian are topics that have recently been receiving much attention. Comparative studies show that all bilaterians share the same core developmental genes, which are organized in gene regulatory networks (GRNs). The conserved GRNs, the "kernels", become linked with downstream genetic circuits, leading to rich and highly hierarchical genetic circuitry (Erwin and Davidson, 2009). Comparison of the DNA of animals belonging to different phyla shows that important morphological and physiological innovations are correlated with additions to and changes in conserved non-coding genetic elements (CNEs). Vavouri and Lehner (2009) focus on *cis*-regulatory enhancers that are located near major developmental genes of kernel genetic networks, and are highly conserved and specific to vertebrates, invertebrate chordates, nematodes, and arthropods. They suggest that these elements may have been the result of duplications and transpositions, that they forged new links between ancient preexisting networks, and were associated with the re-wiring of the genetic circuits underlying the morphological divergence that took place in the Cambrian.

The role of trans-acting regulatory factors, such as miRNAs, has been highlighted by Peterson et al. (2009). They have shown that there is a correlation between the acquisition of miRNAs and morphological complexity: once acquired, miRNAs are not lost, so their accumulation reflects the growth in morphological complexity. They show how miRNA acquisition is correlated with adaptive radiations: for example, during the early Cambrian, when the cnidarians acquired only one miRNA, the nephrozoans accumulated 32 new miRNAs, and during the period in which primates acquired 84 new miRNAs, rodents acquired only 16. The miRNAs are known to both control and stabilize multiple developmental paths (Hornstein and Shomron, 2006), and hence are agents of

both novelty (when they first arise) and canalization (once they become established and expressed at high levels).

CNEs, new miRNAs and other regulatory elements may be generated by transposition, by gene duplications followed by divergence, by hybridization and by lateral gene transfer, for example, following viral infection (Ryan, 2009). The rate of transposition is known to be increased under stress, and both Oliver and Greene (2009) and Zeh et al. (2009) convincingly argue that transposable elements (TEs) increase evolvability: bursts of transposition lead to rapid diversification of lineages and to adaptive radiations, possibly including the Cambrian one. Zeh et al. (2009) argue that periods of stress lead to the activation of transposable elements by suppressing epigenetic silencing mechanisms such as DNA methylation and RNA-mediated silencing, which results in the unleashing of transposition and consequent rapid diversification. The function of the epigenetic control mechanisms in preventing transposition, the growing evidence for the involvement of TEs in generating new genes and new regulators, and the sensitivity of the epigenetic mechanisms to stress, lead to the conclusion that rapid evolutionary diversification is the result of stressful conditions.

Stress does more than unleash transposition. Jablonka and Lamb (2008) and Lamm and Jablonka (2008) have assembled evidence showing that stresses induce local and genome-wide changes in heritable epigenetic marks, which can lead to altered patterns of mitotic and meiotic pairing, to chromosomal re-patterning, to mutation-prone repair, as well as triggering transposition. Stressors can be genomic shocks, such as polyploidization, hybridization, and infection; environmental stresses such as heat, pressure, and changes in nutrition; and stresses mediated by the neurohormonal system, which is the system through which all the responses of animals are mediated (Cabej, 2008). The effects of all these classes of stress may be targeted to particular genomic areas, can affect both morphological and behavioral characteristics, and can be inherited (Jablonka and Raz, 2009).

Although in the early Cambrian, many of the variations induced by the neurohormonal stress resulting from associative learning were likely to have been detrimental, they would also have provided ample material for the selection of mechanisms that enhanced cell memory and hence for the evolutionary sophistication and extent of associative learning itself. Stress-associated learning in extant animals (e.g., aversion-learning or predator avoidance following a painful encounter), which is remembered for a very long time, involves epigenetic re-patterning in the cells of the nervous system. For example, learning and memory consolidation following contextual fear-conditioning involve epigenetic changes in DNA methylation (Miller and Sweatt, 2007) and there are many studies suggesting that learning involves long-term epigenetic modifications in neurons (for a recent review see Mehler, 2008). The evidence for changes in the DNA in neurons as a result of stress-learning are as yet indirect, but some studies on aversion-learning and fear-conditioning suggest that DNA repair and recombination may play a role in the consolidation of the memory of these stressful learnt events (Wang et al., 2003; Colón-Cesario et al., 2006; Saavedra-Rodríguez et al., 2009). There are also suggestions that learned changes, involving RNA editing, are written back into DNA through RNA-mediated repair (Mattick and Mehler, 2008).

It is likely that during the early stages of the evolution of associative learning, the neurohormonal outcomes accompanying and following stress-related associative learning triggered not only persistent genetic and epigenetic changes in nerve cells, but also, as a by-product and in parallel, changes in the germline too. We therefore propose that the long-term effects of hormonal stress on both heritable epigenetic marks and on DNA sequence

organization may have been especially common during the early Cambrian, before the evolution of ameliorating mechanisms which fine-tuned and largely restricted these effects to the neural tissues evolved, but that the traces of these may be still seen in drastic and chronically stressful conditions in extant animals. An important inference that follows from our hypothesis is that the evolution of sophisticated stress response systems resulted in reduced genomic destabilization, which may have been one of the factors that ended the Cambrian radiations.

5. Summary and future directions

We have argued that the emergence of associative learning altered the life and adaptive possibilities of animals. It marked the beginning of a new stage in the history of life, with brains and learning becoming the main engines of animal evolution. The effects of associative learning are compatible with the large changes in morphology and behavior seen in Cambrian metazoans.

Our suggestion that associative learning has been one of the factors driving the Cambrian explosion does not conflict with previous suggestions. It is clear that external changes in temperature, in oxygenation, and in the chemical constitution of the oceans may have provided the necessary permissive conditions for the Cambrian diversification. As we argued, increase in size would have had major effects on the evolution of neural organization, so conditions enabling size increase (we suggested that the oxygenation occurring ~548 Mya was an important factor) would have been necessary for the evolution of associative learning. We assume that the common ancestor of the nephrozoans was a small morphologically plastic animal with a simple nervous system, possibly similar to that seen in acoels. We regard the evolution of hard parts, of eyes, of predation, and of burrowing, as consequences of the evolution of associative learning, and we see basic consciousnesses as an inherent emergent aspect of this type of learning (Ginsburg and Jablonka, 2010). We suggest that initially only minor changes in memory-associated genes were necessary to spur the evolution of associative learning. However, once this type of learning evolved, it contributed to an ecological explosion and to learning-driven genetic accommodation, so our hypothesis is very much in line with the suggestions that the occupation of new ecological niches and new, evolving interactions among species were a crucial part of the Cambrian explosion.

We accept previous suggestions regarding the type of genomic "tools" and architecture that must have been in place for the Cambrian explosion to occur (see Erwin and Davidson, 2009). We also emphasize, as do Zeh et al. (2009), the role of stress in the radiations. However, we have expanded upon some of these arguments, and briefly suggest some additional considerations that follow from our argument. First, as pointed out earlier, stress leads to the generation of transgenerational epigenetic changes in multiple and interrelated ways, not only through the activation of TEs. Second, we believe that neurohormonal stress was an important and persistent stressor during the Cambrian, destabilizing the epigenome, and leading to transgenerational epigenetic responses. Third, selection for persistent, long-term cell memory in neurons, which may have been involved in the evolution of associative learning, may have initially resulted in the parallel induction of non-specific and semi-targeted persistent variations in the germline, a developmental consequence that, through selection, was subsequently ameliorated. Fourth, learning-driven divergence, which led to rapid diversification of lineages, may have resulted in frequent hybridizations, and, depending on the degree of genomic difference between the

partners, to a burst of variations even in the absence of genome duplication, as is seen in extant synthetic plant hybrids (Feldman and Levy, 2009). The occupation of large arrays of new niches may have exposed the animals to different types of bacteria and viruses, and to new types of parasitic and potentially beneficial symbiotic relations, all of which could have elicited genomic defense responses that produced genome re-patterning. Fifth, although we agree with Oliver and Greene (2009) that lineage selection has been important in the evolution of evolvability, and we accept the non-adaptive scenario suggested by Zeh et al. (2009), we believe that the kind of stress-induced heritable genomic adaptation suggested by McClintock (1984) was also involved. As Stern et al. (2007) have shown for yeast cells, novel stressful conditions can launch an intra-organism genomic exploration process in which many gene expression patterns are tried out, but only the functional ones eventually become stabilized and inherited between generations. This type of intra-organism exploration and selective stabilization process may have been important during the initial stages of adaptation to new environments, alongside conventional inter-organism selection among non-adaptively generated re-wired genotypes.

Our argument that associative learning drove the Cambrian explosion opens up new questions, and suggests studies that could reinforce, weaken, or refine the core hypothesis and the assumptions and consequences related to it.

1. Through comparative studies it may be possible to pin-point the molecular tools involved in associative learning and date their origins. Emes et al. (2008) have compared the genomics and proteomics of the postsynaptic density and the membrane-associated guanyl kinase signaling complexes that underlie memory and learning, and found interesting differences between invertebrates and vertebrates. Extending this type of analysis to the synaptic complexity of different invertebrate taxa, especially groups with a nerve net (cnidarians and ctenophores), those with a diffuse nervous system but some anterior centralization (Acoela and the Nematodermatida) and groups with a secondarily decentralized nervous system (echinoderms), and comparing them with groups with fully centralized nervous systems and brains, would be informative. Studying the chromatin conformation of regions involved in the transcriptional regulation of memory-associated genes, the miRNA that evolved in nephrozoans and the targets of these miRNAs in the nervous system, and the genomic targets of epigenetic mechanisms involved in the establishment and maintenance of long-term memory (Levenson and Sweatt, 2005; Wood et al., 2006), could also shed light on the key processes that were modified during the evolution of associative learning. Such comparative molecular studies should make it possible to date the divergence of associatively learning taxa. However, as Pagel et al. (2006) have shown, increased rate of molecular evolution is correlated with periods of speciation: the rate is greater in taxa with phylogenetic trees with multiple nodes than in the trees of related taxa of the same chronological age, but with fewer nodes. Since the Cambrian was undeniably a period of intense speciation, the effects of a high speciation rate would have to be factored into the dating estimates.
2. The role of neural centralization in the evolution of associative learning could be clarified by investigating the learning abilities of echinoderms. Echinoderms are thought to have evolved secondary morphological radialization, so if centralization was and still is necessary for flexible associative learning, echinoderms are expected to have lost some of this learning capacity. If, however, centralization initiated and facilitated the evolution of associative learning, but associative

learning later became dependent mainly on new types of synaptic complexes, and if extant echinoderms possess this new molecular-neural machinery, we expect the associative learning abilities of echinoderms to be similar to those found in other bilaterian groups.

3. Comparative studies of the neural organization and memory-associated gene expression patterns in deuterostomes and protostomes would help to determine whether associative learning evolved in the early Cambrian and occurred in parallel in several bilaterian groups. If it did, we expect to find subtle but consistent differences between the deuterostomes and protostomes, dating to the Cambrian, and, if parallel learning evolution was even more frequent, possibly also within each of these groups.
4. If cnidarians and ctenophores are compared with bilaterian metazoans, our hypothesis predicts that there should be consistent anatomical and molecular differences between them in memory-associated features. We expect instances of associative learning in these groups to be very limited, and, if they exist at all, to depend on the anatomical proximity of the associated neural paths.
5. Investigating cubozoans, a taxon of jellyfish without a brain but with complex multiple eyes underlain by nerve clusters (Nilsson et al., 2005), might show that they had a specialized ability to learn by visual association. We suggest that the cubozoan eye is an evolutionary response to associatively learning animals, and dates to the Cambrian or post-Cambrian era.
6. Neurohormonal stress response systems are expected to be found in all associatively learning animals. We hypothesize that these systems evolved during the Cambrian as a response to the frequent neurohormonal destabilization that animals experienced. We therefore predict that the rapid evolution that occurred in genes involved in the regulation of physiological stress responses will be found to date to the Cambrian. The time it took for these systems to evolve may explain the duration of the Cambrian explosion, and their establishment may be one of the factors that account for the subsequent relative conservatism of morphological evolution.
7. In the neurons of all associatively learning animals, stress-triggered long-term memory is predicted to be linked with persistent epigenetic changes, with transposition, and possibly with other types of DNA-re-patterning that is mediated by epigenetic control mechanisms. We predict that damaging the mechanisms underlying the stress response will lead to a greatly reduced ability to develop long-term memory. This will be reflected in disordered formation of chromatin marks following stress, and unregulated or repressed transposition.
8. Although in extant animals it is likely that neurohormonal destabilization is usually prevented from affecting the germline, we expect that in highly stressful conditions normal controls may break down, and neurohormonal destabilization will be found to have transgenerational effects at both the epigenetic and the genetic (DNA sequence) levels. Such stress-induced breakdown of normal controls may have occurred during the domestication of animals. Belyaev and his colleagues argued that selection for tameability in silver foxes involved the destabilization of the neurohormonal system, which led to multiple effects, including some apparently epigenetic modifications in white spotting which were inherited between generations, and an increased number of supernumerary chromosomes (Belyaev and Borodin, 1982; Trut et al., 2009). We expect that if animals are experimentally exposed to extreme trauma-related learning for several generations, similar transgenerational epigenetic and genetic effects may be found.

There is little doubt that associative learning was a major driving force in the evolution of animals. The investigations we have suggested would all help to evaluate our proposal that it was also an important factor in the Cambrian explosion.

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